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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,524	05/02/2002	Audrey Goddard	P3230R1C001-168	8156

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EXAMINER

SEHARASEYON, JEGATHEESAN

ART UNIT	PAPER NUMBER
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1647

DATE MAILED: 06/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/063,524	Applicant(s) GODDARD ET AL.	
	Examiner Jegatheesan Seharaseyon, Ph.D	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 March 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>3/30/2005</u> . | 6) <input type="checkbox"/> Other: _____ |

Handwritten signature/initials

DETAILED ACTION

1. Upon further consideration the Office Action mailed 6/14/2005 has been vacated.
2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/30/2005 has been entered. An action on the RCE follows.
3. Claims 1-5 are pending.
4. The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office action.
5. Applicants request for correction of inventorship under 37 CFR 1.48(b) is acknowledged.
6. The Office acknowledges the submission of the IDS dated 3/30/2005.

Priority

7. Applicants arguments with respect to the priority has been considered but it is not found to be persuasive. Applicants have not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119. Applicants have argued that they are entitled to the benefit of the filing date of August 24, 2000 based on the disclosure in the PCT Application PCT/US00/23328 filed 8/24/2000 of the differential tissue expression distribution in tumor versus normal tissue (example 18). Although, the previous patent application discloses the same polypeptide (SEQ ID NO: 22) sequence

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and polynucleotides (SEQ ID NO: 21) encoding the polypeptide as the instant specification, the disclosure is not enabling for the instant invention and because the disclosed function does not impart utility to the instant invention for the reasons set forth below and the previous Office Action. Therefore, the filing date of 2 May 2002 is maintained as the priority date.

35 U.S.C. § 101/112, first paragraph, Lack of Utility, Enablement, maintained

8. The rejection of claims 1-5 under 35 U.S.C. 101, as lacking utility is maintained. The reasons for this rejection under 35 U.S.C. § 101 are set forth at pp. 3-8 of the previous Office Action (29 December 2004). Claims 1-5 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office Actions (19 May 2004 and 29 December 2004), one skilled in the art clearly would not know how to use the claimed invention.

The Office acknowledges that the microarray experiments disclosed in the specification (example 18) does measure the level of mRNA expressed in tumor and normal controls. Thus, the Office will not respond to Applicants arguments with respect to both Pennica et al. and Sen et al. references. Applicants argue (30 March 2005, page 6) that the results presented in the instant specification are enabling for the polypeptide of SEQ ID NO: 22 and antibodies directed against polypeptide. They argue that the utilities of PRO1013 polypeptide include the use as a diagnostic tool, as well as therapeutically as a target for treatment, based on the data that PRO1013 cDNA is more highly expressed in normal stomach compared to stomach tumor or tissue.

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Applicants have also extensively discussed the utility guidelines (pages 6-10).

Applicant's arguments (30 March 2005) have been fully considered but are not found to be persuasive for the following reasons:

In the instant case, the specification provides data showing that polynucleotide is more highly expressed in normal stomach compared to stomach tumor tissue counterparts. In addition, blast search provided asserts that PRO1013 is a secreted transmembrane polypeptide. There is no further supporting evidence to indicate that the polypeptide encoded by the polynucleotide of the instant invention is also differentially expressed in the normal tissue compared to the tumor tissue and as such one of skill in the art would conclude that it is not supported by a substantial asserted utility or a well-established utility. Contrary to Applicants assertion that PRO1013 polypeptide is more highly expressed (30 March 2005, pages 12 and 13), Applicants only demonstrate more highly expressed cDNA for PRO1013 in normal stomach compared to stomach tumor tissues counterparts. The argument presented evinces that instant specification provides a mere invitation to experiment, and not readily available utility. There is no description in the specification to that would indicate a correlation with higher expression levels of the message to the PRO1013 polypeptide. It remains that, there is no information on the record as to whether the claimed protein is expressed at all in the skin tissue, cancerous or otherwise.

Given the increase in message (cDNA) for PRO1013 in the normal stomach or compared to stomach tumor tissue, and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that a more highly expressed

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mRNA would directly correlate with increased polypeptide levels. Thus, a role for the antibody of the instant invention in the diagnosis and/or treatment of cancers is not clear. Further research needs to be done to determine whether the increase of PRO1013 cDNA in normal stomach compared to stomach tumor tissue supports a role for the polypeptide in the cancerous tissue; such a role has not been suggested by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. As discussed in *Brenner v. Manson*, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and,

"a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the Specification's assertions that the claimed antibodies directed to PRO1013 polypeptides have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

Haynes et al (1998, *Electrophoresis*, 19: 1862-1871) and Hu et al. (2003, *Journal of Proteome Research* 2: 405-412) were discussed previously in the Office Action dated 29 December 2004. Chen et al. (2002, *Molecular and Cellular Proteomics* 1: 304-313) disclose that twenty-eight of the 165 protein spots (17%) or 21 of 98 genes (21.4%) had

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a statistically significant correlation between protein and mRNA expression (abstract). In addition, it is stated that no significant correlation between mRNA and protein expression was found ($r=-0.025$) if the average levels of mRNA or protein among all samples were applied across the 165 protein spots (98 genes). The reference also teaches that the mRNA/protein correlation coefficient also varied among proteins with multiple isoforms, indicating potentially separate isoform-specific mechanisms for the regulation of protein abundance. In this study using a quantitative analysis of mRNA and protein expression within the same lung adenocarcinomas, it is showed that only a subset of the proteins exhibited a significant correlation with mRNA abundance. Gygi et al. (1999, PTO1449 of 3/30/05) determined the correlation between mRNA and protein expression levels for selected genes expressed in yeast. It was found that the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data (abstract).

Contrary, to Applicants assertion that Haynes et al. does not contradict the utility and enablement of the instant claims (page 16 of the response), Haynes et al. states that "These results suggests that even for a population of genes predicted to be relatively homogeneous with respect to protein half-life and gene expression, the protein levels cannot be accurately predicted from the level of the corresponding mRNA" (page 1863, 2nd paragraph). Although, Applicants assert that there is a strong correlation between mRNA expression Gygi et al. conclude that transcript levels provide little predictive value with respect to the extent of the protein expression (page 1730, last line). Contrary, to Applicants assertion that Hu et al.'s methodology provide little or no

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information regarding biological significance of genes with less than 5-fold expression change in disease, the reference teaches that "careful hunt for corroborating evidence of a role in breast cancer should precede any further study of genes with less than 5-fold expression level change".

Orntoft et al. "*could only compare the levels of about 40 well-resolved and focused abundant proteins*"(page 42). The reference Orntoft et al. has not provided any information that would correlate the low levels of DNA amplification found in majority of tested tumors and the associated levels of the encoded proteins. The Hyman reference cited by applicants found 44% of *highly* amplified genes showing overexpression at the mRNA level, and 10.5% of highly overexpressed genes being amplified; thus, even at the level of high amplification and high overexpression, the two (mRNA and protein) do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Office maintains that 2% does not provide a reasonable expectation that the slight amplification of SEQ ID NO: 32 would be correlated with elevated levels of mRNA. Further, Hyman does not examine protein expression. Applicants are reminded that the instant claims are directed to antibodies that bind the protein. Similarly, Pollack, cited by applicants, does not analyze protein levels, nor does Pollack support the assertion that it is predictable, on the basis of the minimal increase in mRNA levels that the protein would accordingly be found at altered levels. Accordingly, it remains that the significance of the gene amplification data is questionable, and cannot be predictably extrapolated as applying to the claimed

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protein. The art, taken as a whole, clearly teaches that it is not predictable that a two-fold message increase in the nucleic acid would translate to detectable over-expression of the associated mRNA, much less any protein encoded thereby. Further, as evidenced by the Orntoft publication, the type of data presented in the instant specification clearly does not meet the standard in the art for establishing association of a protein with cancer.

The declarations of Mr. Grimaldi, Dr. Polakis and Dr. Ashkenazi filed under 37 CFR 1.132 were considered previously considered in the Office Action dated 29 December 2004. The declarations were found to be insufficient to overcome the rejection of claims 1-5, based upon 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the Office Action dated 19 May 2004 and 29 December 2004. Applicants' arguments have been fully considered but are found to be persuasive.

In the declaration filed under 37 CFR 1.132 (30 March 2005, originally filed in application serial number 10/063,557), senior research associate Mr. Grimaldi has asserted that, if a difference in mRNA is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor tissues. It is further stated that additional studies can then be conducted if further information is desired. In paragraph 7, declarant indicates that the difference in the expression is expected to be reflected in the difference in the corresponding protein. However, there is no description in the specification to that would indicate a correlation with higher or lower expression levels of the message to the PRO1013 polypeptide.

Applicants further citing the second Grimaldi declaration (exhibit 2) filed under 37 CFR § 1.132 argues that, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed..... this same principal applies to gene under-expression." Citing paragraph 5, Applicants contend that "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for the diagnosis and treatment."

At paragraph 4 of the second Grimaldi declaration (Exhibit 2), the declarant discusses mutations of Her2/Neu, and chromosomal translocations that are known to be associated with cancer, and states that "If the chromosomal aberration results in the aberrant expression of a mRNA and the corresponding gene product (the polypeptide) as they do in the aforementioned cases, then the gene product is a promising target for cancer therapy, for example, by the therapeutic antibody approach." This argument has been fully considered but is not deemed persuasive because it evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO1013 gene, unlike Her2/Neu, has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. Similarly, unlike t (5;14), no translocation of PRO1013 gene is known to occur. All that the specification demonstrates is that the PRO1013 nucleic acid (mRNA) was more highly expressed in normal stomach compared to stomach tumor tissues counterparts. No mutation or translocation of PRO1013 gene has been associated with for example,

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stomach tumor. Therefore, in the absence of any of the above information, all that the specification does is present evidence that the mRNA encoding PRO1013 is more highly expressed in an unknown number of samples, and invite the artisan to determine the rest of the story. Such is insufficient to meet the requirements of 35 U.S.C. § 101 for the claimed antibodies binding the PRO1013 polypeptide.

The Polakis declaration states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr Polakis characterizes the instances where such a correlation does not exist as exceptions to the rule.

The specification describes only mRNA expression data. The argument presented evinces that instant specification provides a mere invitation to experiment, and not readily available utility. Furthermore, as indicated above the literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue (see Hu et al discussions above). It is also not known whether PRO1013 polypeptide is expressed in normal stomach tissue. There is no nexus between the mRNA expression and PRO1013 polypeptide or antibodies binding PRO1013 polypeptide. In the absence of any of the above information, all that the specification does is present evidence that the mRNA encoding PRO1013 is present at higher levels in normal stomach compared to stomach tumor tissue counterparts, and invite the artisan to determine the rest of the story. This is further borne out by Grimaldi assertion that "additional studies can then be conducted

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if further information is desired" (Appendix A, paragraph 7). Such is insufficient to meet the requirements of 35 U.S.C. § 101 utility for the claimed antibodies.

Although, Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide, it is important to note that the instant specification provides no information regarding protein levels. Only mRNA expression data was presented. Therefore, the declaration is insufficient to overcome the rejection of claims 1-5 based upon 35 U.S.C. § 101 and 112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels. Furthermore, the declarations do not provide data such that the examiner can independently draw conclusions. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue, as discussed above in Hu et al. In addition, as discussed above Haynes et al., Chen et al. and Gygi et al. disclose that the correlation between mRNA expression and protein expression is poor at best.

Applicants also contend that the claimed antibodies would have diagnostic utility even if there is no positive correlation between gene expression and expression of the encoded polypeptide. Applicants assert that this position is supported by the declaration filed under 37 CFR 1.132 (30 March 2005) by staff scientist Ashkenazi. It claims that the purpose of the experiments that measured increases in gene copy number was to identify tumor cell markers useful for cancer treatment (pages 1-2, Declaration, 18

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March 2005) and to identify cancers for which there was an absence of gene product over-expression (page 2).

The declaration of Ashkenazi appears to argue that even if there was no correlation between gene expression and increased or decreased protein expression for PRO1013, the polypeptide encoded by a gene that is over-expressed or under expression in cancer would still have credible, specific and substantial utility. The examiner agrees that evidence regarding lack of over-expression would be useful. However, there is no evidence as to whether the gene products (such as the polypeptide) are over-expressed or not in the instant invention. Further research is required to determine such. Thus, the asserted utility is not substantial.

Applicants along with Mr. Grimaldi, Dr. Polakis and Ashkenazi declarations, Applicants also provide teachings from Molecular Biology of the Cell by Bruce Alberts and Genes VI (1997) by Ben Lewin, to support their assertion that there is a correlation between increased gene expression and increased protein expression (page: 19 and 20). Applicants also refer to additional articles by Zigang et al., and Meric et al. as providing evidence that gene amplification generally results in elevated levels of the encoded polypeptide. Zigang et al. describe a specific example of the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as potential molecular target for diagnosis and treatment of human prostate cancer. It is asserted that the data shows "a high degree of correlation between PSCA protein and mRNA expression". Further Meric et al. states that "the fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer

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cells and normal cells. Meric et al also teaches that most efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. It further states that gene expression is quite complicated, however, and is also regulated at the level of mRNA stability, mRNA translation and protein stability. Further reading of Meric et al. casts doubts on Applicants claim that there is a direct correlation between increased mRNA levels and the level of expression of the encoded protein. For example, the reference discusses that variations in mRNA sequences increase or decrease translational efficiency as found in BRCA1 (see pages 973-974). In addition, advances in technology allowing comparisons of message and protein using proteomics show a lack of correlation as evidenced by Haynes et al., Chen et al., and Gygi et al.

Applicants argue (Response, 30 March 2005, page 14) that even if a prima facie case of lack of utility has been established, it should be withdrawn on consideration of the totality of the evidence. Applicants provide evidence in the form of a publication by Hanna et al. (attached to the Response of 18 March 2005). Applicants contend that the publication teaches that the HER-2/neu (c-erbB2) gene is over-expressed in breast cancers, and teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene as well as over- expression of the HER-2/neu gene product. Applicants argue that the disclosed assay leads to a more accurate classification of the cancer and a more effective treatment of it. The examiner agrees. In fact, Hanna et al. supports the instant rejection, in that Hanna et al. show that gene

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amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically.

Applicants claim regardless of the cause of the differential expression, the fact that there is a higher level or lower level of expression PRO1013 gene in normal stomach compared to stomach tumor tissues counterparts allows this mRNA expression to be used as a diagnostic tool. These arguments have been fully considered but are found to be partially persuasive because the Office accepts that aneuploidy has no relevance to the differential expression of the mRNA of the instant invention. However, the lack of information on the record whether the claimed protein (PRO1013) is expressed at all in normal stomach tissues, cancerous or otherwise would make significant further research a necessity.

At page 10, Applicants assert that they have established that the accepted understanding in the art is that there is a direct correlation between mRNA levels and the level of expression of the encoded protein. Haynes et al. and Chen et al. teachings listed above and discussed contradict Applicants assertion that there exists a direct correlation between mRNA levels and the level of expression of the encoded protein. In fact, the literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissues. Therefore, there is no evidence to support Applicants' assertion that there is working hypothesis among those skilled in the art is that there is a direct correlation between mRNA levels and protein levels. The declarations and cited references do not establish a substantial utility for the claimed antibodies binding PRO1013 polypeptide molecules.

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As stated above, the specification does not provide sufficient guidance to the skilled artisan to diagnose or treat any disease.

A utility such as cancer research would in fact be specific to the polypeptide. However, further research is required to ascertain whether the protein levels of PRO1013 are altered and thus provide a substantial, that is, real-world and reasonable confirmed, utility. Therefore, all of these reasons, the rejection of claims 1-5 based upon 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the last Office Action is maintained.

9. No claims are allowed.

10. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Contact information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 571-272-0892. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JS 06/05


JANET ANDRES
PRIMARY EXAMINER